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EXAMINER	
BOESEN, AGNIESZKA	

ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
02/04/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/550,198	VISVANATHAN ET AL.	
	Examiner	Art Unit	
	AGNIESZKA BOESEN	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81-92,137 and 138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-92,137 and 138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/14/2007 and 3/16/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received July 7, 2009 and November 16, 2009.

Election/Restrictions

Applicant's election of group II, claims 81-92 and the species of Hepatitis B virus and TLR-2 is acknowledged. New claims 137 and 138 read on the elected invention and are examined together with group II claims 81-92.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 81-92, 137 and 138 are under examination in this Office Action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 9/14/2007 and 3/16/2007 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner.

Claim Objections

Claim 86 is objected to because of the following informalities: The claim recites "Hepatitis B virus (HBV)" twice. Applicant is required to correct the typographical error.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 92 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 92 recites the limitation "said pathogenic agent". There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 81-92, 137 and 138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are drawn to a method for monitoring a response to a therapeutic protocol to prevent infection and to prevent a disease condition comprising determining the level of Toll-like receptors and their homologs wherein the efficacy of the therapeutic response is determined by a change in the level of the Toll-like receptors.

The claims are rejected because the present specification does not provide sufficient written description for a genus of Toll-like receptor homologs used in the claimed methods.

The claims are rejected because Applicant's disclosure does not provide sufficient evidence that Applicant was in possession of a representative number of Toll-like receptor homologs. The claims require that the claimed method comprises determining the level of Toll-like receptor homologs, while the specification does not name any representative species of the Toll-like receptor homologs. The art teaches that TLR-2 expression is significantly increased in patients with cirrhosis and that the TLR-4 expression is not significantly different in those patients (see Riodan et al. Hepatology, 2003, Vol. 37, p. 1154-1164). The art teaches that small anti-viral compounds activate immune cells via TLR-7 dependent signaling pathway (see Hemmi et al. Nature Immunilogy, 2002, Vol. 3, p. 196-200 and Akira et al. Immunology Letters, January 2003, Vol. 85, p. 85-95). The art does not teach Toll-like receptor homologs that are involved in infection and could possibly be measured in the claimed methods.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the specification contemplates a genus of Toll-like receptor homologs. Accordingly, in the absence of insufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed structures of the compounds encompassed by the genus of Toll-like receptor homologs that should be useful in the claimed methods. For the written description requirement, an applicant's specification must reasonably convey to those skilled in the art that the applicant was in possession of the claimed invention as of the date of invention. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997); *Hyatt v. Boone*, 146 F.3d 1348, 1354, 47 USPQ2d 1128, 1132 (Fed. Cir.1998).

The skilled artisan cannot envision the detailed structures of Toll-like receptor homologs used in the claimed methods. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the invention as presently claimed.

Claims 81-92, 137 and 138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make, and/or use the invention.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988). The factors that may be considered include (1)

the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors deemed relevant are those of the amount of direction and the working examples provided, that quantity of experimentation necessary, the (un)predictability of the art, and the breadth of the claims.

Claims are drawn to a method for monitoring a response to a therapeutic protocol to prevent infection and to prevent a disease condition comprising determining the level of Toll-like receptors and their homologs wherein the efficacy of the therapeutic response is determined by a change in the level of the Toll-like receptors.

The claims are rejected because the present specification does not provide sufficient enabling disclosure to practice the broad scope of the claimed methods with regard to a genus of **1)** infections, **2)** a large number of pathogens in claims 86 and 92, **3)** the genus of diseases, **4)** all known Toll-like receptors or **5)** Toll-like receptor homologs. The present specification does not enable the claimed method for monitoring the response to a therapeutic protocol to **6)** prevent infection by a pathogenic agent or to **7)** prevent the development of a disease condition.

The claims are broadly drawn to any infection, any pathogenic agent and any disease condition. The claims require determining the level of Toll-like receptor homologs.

The present specification discloses correlation between HBV and HCV infection and TLR-2 expression. Example 1 shows up-regulated expression of TLR-2 and TLR-4 on CD14

monocytes in HCV infected patients. Example 2 discloses that TLR-2 expression is significantly reduced in chronic hepatitis B patients and that TLR-2 expression normalizes in lamivudine treated chronic hepatitis B patients and that hepatitis B down-regulates expression of TLR-2 on PBMCs. The specification speculates that the HBV-induced defect in innate immunity contributes to the development of persistent infection. Example 5 contemplates that subjects potentially exposed to HBV can be screened for their levels of TLR-2 and/or TLR-4 prior to therapeutic intervention and when a subject exhibits a change in the level of TLR-2 and/or TLR-4 during early phase treatment (i.e. a trend to normalization of levels of TLR-2 and/or TLR-4) this predicts that the therapy is working. The specification does not disclose working examples showing that one of skill in the art can in fact monitor a response to a therapeutic protocol to prevent infection with a pathogenic agent or to prevent development of disease comprising determining the level of TLR receptors or their homologs.

The art teaches that TLR-2 expression is significantly increased in patients with cirrhosis and that the TLR-4 expression is not significantly different in those patients (see Riodan et al. Hepatology, 2003, Vol. 37, p. 1154-1164). The art teaches that small anti-viral compounds activate immune cells via TLR-7 dependent signaling pathway (see Hemmi et al. Nature Immunilogy, 2002, Vol. 3, p. 196-200 and Akira et al. Immunology Letters, January 2003, Vol. 85, p. 85-95).

As discussed above the present claims encompass a genus of pathogens and a genus of diseases. There is no evidence in the art that any infection and any disease correlates with the change in TLR expression or that any medical therapy can influence the levels of TLR expression. The skilled artisan would have to conduct an undue amount of experimentation in

order to positively conclude that by determining the level of TLR receptors and their homologs one of skill in the art could monitor the response to a therapeutic protocol to prevent infection or disease.

In conclusion, in view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in specification, and the breadth of the claims, it would take undue trials and errors to practice the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 81, 83-85, 87, 89-91 are rejected under 35 U.S.C. 102(e) as being anticipated by Renshaw et al. (Journal of Immunology, 2002, Vol. 169, p. 4697-4701).

Claims are drawn to a method for monitoring a response to a therapeutic protocol to prevent infection and to prevent a disease condition comprising determining the level of Toll-like receptors wherein the efficacy of the therapeutic response is determined by a change in the level of the Toll-like receptors.

It is noted that the recitation of the intended use recited in the preamble of the claimed method is not given patentable weight. A preamble is generally not accorded any patentable

weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Additionally, it is noted that the "wherein" clause is not considered to further limit the claimed method steps. See Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

The only active/positive method step recited in the present claims is determining the level of Toll-like receptors.

Renshaw discloses determining the level of expression of TLR-2 and TLR-4 on splenic macrophages by analyzing the mRNA and protein and discloses that the decline in TLR expression and function correlates with increased susceptibility to infection and poor adaptive immune response (see the entire document, particularly Materials and Methods and Figures 1-3).

Thus by this disclosure Renshaw anticipates the present claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 81-92, 137 and 138 are rejected under 35 U.S.C. 102(e) as being unpatentable over Renshaw et al. (Journal of Immunology, 2002, Vol. 169, p. 4697-4701) in view of Akira et al. (Immunology Letters, January 2003, Vol. 85, p. 85-95).

Renshaw teaches determining the level of expression of TLR-2 and TLR-4 on splenic macrophages by analyzing the mRNA and protein and discloses that the decline in TLR expression and function correlates with increased susceptibility to infection and poor adaptive immune response (see the entire document, particularly Materials and Methods and Figures 1-3).

Renshaw does not teach comparing the level of TLR expression to the pre-treatment sample and to the control sample. Renshaw does not teach pathogenic agents recited in claims 86 and 92.

Akira teaches various pathogenic ligands recognized by the Toll-like receptors, the pathogens are Klebsiella, Chlamydia, Neisseria, Streptococcus, and viruses in general (see Table 1). Akira teaches that the antiviral and the anti-cancer compound imidazoquinoline used for

treatment of HCV, Papilloma and Herpes virus infection activate immune cells via Toll-like receptor 7 (see page 90).

It would have been *prima facie* obvious to provide a method for monitoring a response to a therapeutic protocol comprising determining the level of expression of TLR receptors and comparing the TLR expression level to the pre-treatment sample and the control sample.

One would have been motivated to provide a method for monitoring a response to a therapeutic protocol to study the disease condition or infection comprising determining the level of expression of TLR receptors because Akira teaches various pathogenic ligands recognized by the Toll-like receptors, the pathogens are Klebsiella, Chlamydia, Neisseria, Streptococcus, and viruses in general (see Table 1) and teaches that the antiviral and the anti-cancer compound imidazoquinoline used for treatment of HCV, Papilloma and Herpes virus infection activate immune cells via Toll-like receptor 7 (see page 90).

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 81-92, 137 and 138 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 7 and 12 of copending Application No. 11/597,063.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of this application are drawn to a method for monitoring a response to a therapeutic protocol to prevent HBV infection comprising determining the level of Toll-like receptors wherein the efficacy of the therapeutic response is determined by a change in the level of the Toll-like receptors and the claims of the copending application are drawn to a method for monitoring effectiveness of a therapeutic protocol directed against HBV infection comprising determining the level of TLR-2. The claimed methods and the methods of the copending application are drawn to the same method and comprise the same method steps. Thus the claimed methods are obvious in view of the claims of the copending application.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AGNIESZKA BOESEN whose telephone number is (571)272-8035. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached at 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Agnieszka Boesen/
Examiner, Art Unit 1648